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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/718,495	O'KEEFE, THERESA L.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16 and 20-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-16 and 20-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 3/31/06 are pending.

2. Applicant's election of Group V, claims 15-16 (now claims 15-16 and 20-33) drawn to a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade, comprising administering to the patient an effective amount of a polypeptide comprising a high mobility group box protein (HMGB) A box and the HMG1L1 as the species filed on 3/31/06, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 15-16 and 20-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 15-16, 23 and 30 are indefinite in that they only describe the compositions of interest by an arbitrary protein name, "HMG1B1 A box". While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein. For example, others in the field may isolate the same protein and give it an entirely different name. Applicant should particularly point out and distinctly claim the "HMG1B1 A box" by claiming a sufficient number of characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.) to distinctly identify the "HMG1B1 A box" protein. Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and of what compositions comprising that protein are made. Further, the NCBI data can be updated to have new version of sequence.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-16 and 20-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide **enablement** for a method of treating any "condition in a patient characterized by activation of an inflammatory cytokine cascade", comprising administering to the patient an effective amount of a polypeptide comprising any "high mobility group box protein (HMGB) a box or variant thereof" which can inhibit release of a proinflammatory cytokine from any "cell", wherein said HMGB A box is any "HMG1B1 A box" in claim 15, or any "condition in a patient characterized by activation of an inflammatory cytokine cascade", comprising administering to the patient an effective amount of a polypeptide , wherein said polypeptide is any "high mobility group box protein (HMGB) a box or variant thereof" which can inhibit release of a proinflammatory cytokine from any "cell", wherein said HMGB A box is any "HMG1B1 A box" in claim 16, wherein the condition is sepsis in claims 20 and 27, rheumatoid arthritis in claims 21 and 28 or endotoxic shock or allograft in claims 22 and 29, wherein HMG A box is an HMG1L1 A box in claims 23 and 30, the methods further comprising administering an antagonist of an early sepsis mediator in claims 25 and 32, wherein the antagonist is an antagonist of TNF in claims 26 and 33. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

There is insufficient guidance and direction as to make and use any "condition in a patient characterized by activation of an inflammatory cytokine cascade". Furthermore, the specification fails to provide in vivo data to show that method would work. Finally, the specification fails to show any HMGB A box polypeptide including the one encoded by pseudogenes would work.

The claims require a method for treating any condition in a patient characterized by activation of an inflammatory cytokine including sepsis, rheumatoid arthritis, endotoxic shock and allograft rejection, comprising administering an effective amount of HMGB A box polypeptide or variant thereof which can inhibit release of a proinflammatory cytokine from a cell.

However, the specification does not provide sufficient enablement to treat for example GVSD caused by a Th1 cell-mediated immune response or by a Th2 cell mediated immune response. Dallman MJ (Current opinion in Immunology 7:632-638, 1995) teaches that both Th1 and Th2 cells are involve in graft rejection response. Dallman concluded that it is difficult to make a case that graft rejection is caused by an immune response driven by either Th1 or Th2 cells alone (see page 632 under Does the Immune response leading to graft rejection involve both Th1 and Th2 cells? in particular). Krenger and Ferrara (immunol. Res. 15:50-73, 1996) describe the development of acute graft-versus-Host disease as a three-step process. Specially, donor T cell activation during the second step of Graft-versus-Host Disease pathophysiology is characterized by proliferation of type 1 T cells and secretion of Il-2 and IFN-γ. Moreover, Krenger and Ferrara teach that distinct immunological patterns observed in two murine models of a cute and chronic graft-versus-host disease are associated with differential activation of Type I and type 2 T cell subsets after allogeneic BMT (see page 61, 2nd col., lines 29-33). Further, Krenger and Ferrara et al teach that a classical lethal acute GVHD is linked to the preferential activation of donor T cells secreting Il-2 and IFN-γ which the less severe chronic form of GVHD is characterized a type 2 cytokine response where IL-4 and IL-10 are preferentially produced after BMT (see page 61, 2nd

col., lines 38-43 and page 62, lines 1-10). Thus, the specification does not provide sufficient enablement for the treat the both chronic and severe lethal acute GVSD syndrome.

Also, Friend et al (Transplantation 68:1625-1631, 1999) teach that monoclonal antibodies have proved to be of immense importance from a diagnostic and investigative standpoint. However in clinical transplantation their impact on therapeutic regimens has been rather disappointing (see 1st col., 1st paragraph).

Further, the specification fail to provide guidance on which organ can be transplanted using claimed method. The specification does not provide sufficient enablement for transplanting any organ or any tissue rejection. Toogood et al (Transplantion 62:851-855, 1996) teaches that the mechanisms of rejection in small bowel and other solid organ grafts are likely to be different (see abstract in particular). Importantly, Toogood et al concluded that there are significant immunological differences between the gut wall compartment of a small bowel transplant and other vascularized allografts (see page 855, 1st col., lines 13-16 in particular). Therefore, it is not clear that the skilled artisan could predict the efficacy of the "HMGB A box" to treat any condition including any organ or tissue rejection.

Regarding sepsis, Freeman *et al* teaches that mediator-specific antagonists, high dose glucocorticoids, and endotoxin-directed therapies, were administered initially in animal models with promising results. Their administration to human, however, proved disappointing, prompting questions regarding both the initial hypothesis and the value of animal studies in modeling human sepsis. Freeman *et al* further teach that many issues pertaining to the pathophysiology and treatment of sepsis remain unresolved (see page 973-974, under conclusion). Due to the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed composition with a reasonable expectation of success.

Further, claim 15 reads on the full-length of HMGB because the claim recites "comprising" which is an open-ended term. However, the specification on fig.1 and page 54, lines 8-12 discloses that the wild-type HMGB1 significantly *stimulated* TNF release by monocytes cultures. Therefore, it cannot be seen how a polypeptide comprising the HMGB A box, which reads on the full-length, would *inhibit* release of a proinflammatory cytokine from a cell.

Claims 15 and 16 recite HMGB A box variants, however, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases and recognized that it was unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences.

Moreover, claims 15, 16, 23 and 30 recite the HMGB A box polypeptide of HMG1L5 A box, HMG1B1 A box, HMG1L4 A box, BAC clone RP11-395A23 A box, HMG1L9 A box, LOC122441 A box, LOC139603 A box and HMG1L8 A box. The specification discloses that

the two HMGB boxes are highly conserved 80 amino acid, L-shaped domains (see page 3, line 15). Further, the specification on Fig 12D, discloses the amino acid sequence of a human, mouse, and rat HMG1 A box polypeptide as SEQ ID NO:4. However, the HMGB1 related sequences are encoded by pseudogenes or very similar genes (see Rogalla et al Cytogenet Cell Genet. 1998, 83:124-129). Pseudogenes are areas in the genome that look like real genes but do not function (non-functional copies). Furthermore, the literature classifies HMG1L1, for example, as paralog of HMGB1, indicating that HMG1L1 evolves new functions. The specification fails to show that those non-functional polypeptides encoded by the pseudogenes represent a functional HMGB A box that would inhibit release of a proinflammatory cytokine from any cell. While the specification under examples 6 and 7 discloses that A box protein inhibits full length HMGB1 and HMGB1 B box cytokine activity, however, the specification fails to disclose which "HMGB A box" was used in the *in vitro* as antagonist of HMGB1 activity in the macrophage culture experiments to inhibit the TNF-stimulating activity of HMGB1.

Example 7 discloses that HMGB1 A box protein inhibits HMGB1 cytokine activity by binding to HBGB1. This indicates that the recited HMGB A box are encoded by pseudogenes or very similar genes are ligands-protein interaction. However, it is recognized in the art that ligands must posses significant structural and chemical complementarity to their target receptors (Kuntz, Science, 1992, Vol. 257:1078-1082, especially page 10709, 2nd col., lines 1-4 and 9-12 under heading "Structure-Based Design) and that ligands generally bind to native states of proteins with little or no interaction with unfolded states (Miller et al, Protein Science, 1997, 6:2166-2179, especially page 2166, 2nd col., lines 18-20) and further that alterations in protein structure lead to alterations in bindings affinity proportional to the magnitude of the alteration (Miller et al, abstract, lines 2-4). Finally, Kuntz teaches that as little as 2% of compounds predicted to inhibit specific enzymztic or receptor systems actually shown inhibition in the micromolar range (page 1080, 3rd col.). The claims encompass alterations in protein folding because claims do permit deviation from the amino acid sequences of the HMGB1 A box form a non-native protein. It would be reasonable to conclude that alterations in protein folding would lead to a large alteration in binding affinity.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the method of inhibiting the release of cytokine indices HMGB A box such as cytokine-based molecules can be species – and model-dependent, it is not clear that reliance on the HMGB1 A box that inhibits HMGB1 cytokine activity by binding to it (Examples 6 and 7of the instant specification) accurately reflects the relative efficacy of the claimed "method of treating" in a subject by active immunization with HMGB1 A box polypeptide.

Finally, claims 25 and 32 recite an antagonist of an early sepsis mediator. However, besides the TNF antagonist, the specification fails to disclose what are those early sepsis mediators.

The instant claims are drawn to a large genus of methods which have not been developed yet to the point where a specific benefit exists in currently available form. Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention,

the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e1) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

8. Claims 15-16, 20-22, 24-29 and 31-33 are rejected under 35 U.S.C. 102(e1) as being anticipated by US/2003/0060410 A1.

The `410 publication teaches and claims a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade comprising administering to the patient a polypeptide comprising a vertebrate high mobility group protein (HMG) A box or a non-naturally occurring HMG A box (all are HMGB A box variants to the claimed HMGB A box) which can inhibit release of a proinflammatory cytokine from a vertebrate cell treated with high mobility group (HMG) protein in an amount sufficient to inhibit release of the proinflammatory cytokine from the cell (see published claims 15-16 in particular). The `410 further teaches that a composition comprising any of the polypeptides can inhibit a condition characterized by activation of an inflammatory cytokine cascade. The condition can be one where the inflammatory cytokine cascade causes a systemic reaction, such as with endotoxic shock, rheumatoid arthritis, allograft rejection or sepsis (see paragraph 98 in particular). Also, the `410 publication teaches that the composition can further comprise an antagonist of an early sepsis mediator. The antagonist of an early sepsis mediator is preferably an antagonist of a cytokine selected from the group consisting of TNF, IL-1.alpha., IL-1.beta., MIF and IL-6, more preferably, an antibody to TNF or MIF, or an IL-1 receptor antagonist (see paragraph 12 in particular).

The reference teachings anticipate the claimed invention.

9. Claims 15-16 and 20-33 are rejected under 35 U.S.C. 102(e1) as being anticipated by US/2003/0144201 A1.

The `201 publication teaches and claims a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade comprising administering to the patient a polypeptide comprising/is a vertebrate high mobility group protein (HMG) A box or a non-naturally occurring HMG A box which can inhibit release of a proinflammatory cytokine from a vertebrate cell treated with high mobility group (HMG) protein in an amount sufficient to inhibit release of the proinflammatory cytokine from the cell (see published claims 15-16 in particular), wherein the HMG A box is published SEQ ID NO: 25 (claimed HMG1L1 A box) (see Fig. 14D in particular). The `201 publication further teaches that a composition comprising any of the polypeptides can inhibit a condition characterized by activation of an inflammatory cytokine cascade. The condition can be one where the inflammatory cytokine cascade causes a systemic reaction, such as with endotoxic shock, rheumatoid arthritis, allograft rejection or sepsis (see paragraph 120 in particular). Also, the `201 publication teaches that the composition can further comprise an antagonist of an early sepsis mediator. The antagonist of an early sepsis mediator is preferably an antagonist of a cytokine selected from the group consisting of TNF, IL-1.alpha., IL-1.beta., MIF and IL-6, more preferably, an antibody to TNF or MIF, or an IL-1 receptor antagonist (see paragraph 13 in particular).

The reference teachings anticipate the claimed invention.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

April 27, 2006

Maher Haddad

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